

REMARKS

Claims 24 to 27, 29, 35, 38 to 40, 62 to 73, 77 to 84, 86 to 101, and 104 to 105 are in the application. Claims 1 to 23, 28, 30 to 34, 36, 37, 41 to 61, 74 to 76, 85, 102 and 103 have been cancelled. Claims 24, 27, 35, 62, 63 to 67, 78, 84, 86 and 93 have been amended. Claims 104 and 105 added. Support for the newly added claims lies in the specification on page 34, lines 3 and 4. No new matter is believed added. Applicants reserve the right to file continuation application on deleted or cancelled subject matter.

The various amendments correct typographical errors, provide support for lack of antecedent basis in the dependent claims, and find support in the original claims as filed. For instance, Claim 24 incorporates the subject matter of claim 28 (cancelled) wherein the active agent is dextromethorphan. Claim dependencies in claims 35, 65, 66 and 86 have been amended. Claim 84 now incorporates the particle size limitations of claim 85 (cancelled).

**Rejections under 35 USC §112, second paragraph**

Claims 1 to 103 are rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Various claims have been cancelled rendering the rejections thereto moot.

Claim 67 has been amended to include the term "further" as suggested by the Examiner.

Claim 93 has not been amended as suggested as it is believed unnecessary since claims 24 and 27 have been amended to recite dextromethorphan as the active agent, thereby obviating this rejection.

Reconsideration and withdrawal of the rejection to the claims under 35 USC §112 is respectfully requested.

**Rejection under 35 USC §102**

Claims 1 to 3, 5 to 7, 11 to 13, 21 to 31, 38, 58 and 61 are rejected under 35 USC §102(b) as being anticipated by Oshlack et al., US 5,472,712. Applicants respectfully traverse this rejection.

Claim 1 of the '712 patent requires a curing of the coated substrate (i.e. the pellets or beadlets)" in a relative humidity of from about 60% to about 100% for a sufficient period of time". Claim 11 set the relative humidity at 85%. Claim 10 sets the cure time from about 48 to about 72 hours.

In contrast, Applicants process does not require a curing of the finished product to be under humidifying conditions. Applicants also do not require a curing time of 2 to 3 days. Applicants have found that it is only necessary to cure the product at a temperature which is raised to about 60°C, and is held there for about 1 hour. At this temperature, the ethylcellulose (as contained in the Surelease® product) is above its glass transition temperature ( $t_g$ ) and is in a rubbery state and rather "sticky". The beadlet has a top coat which provides an outer layer that allows the product to be cured and not stick to each other while maintaining discrete, fluidized particles in the coating unit. The top coat does not effect the curing of the polymerized coat of ethylcellulose.

Applicants have found, unexpectantly, that this will reduce the curing time from the process of the '712 patent from almost 3 days to about one hour, and that this process will not require increased humidifying conditions, just an increased temperature control for a relatively short period of time, (see page 30 of the specification, lines 8-9 and original claim 100). These two attributes alone greatly enhance the commercial aspects and decreased costs associated with the claimed process. This is not taught by the '712 patent.

Another difference in the process of '712 patent and Applicants is in the drug loading of the beadlets. Oshlack et al. only coats the substrate (i.e. the sugar spheres, etc.) with a 2 to about 30% w/w of drug. In contrast, Applicants can, and have coated the spheres with a much higher drug load of the claime active, dextromethorphan (DXM). See for instance Example 10, which produces a beadlet layered with 47% w/w of DXM. Applicants have further provided for in the specification, pages 25 to page 30, line 4 various problems encountered with the manufacture of DXM pellets. It has been very difficult to obtain a sufficient drug load of DXM active on the spheres (page 25, lines 9 to 35) as well as having consistent solubility of the DXM in the environmental fluids.

Applicants have unexpectedly found that by micronizing the DXM particles they can produce a pellet which has a sufficient drug load, in a commercially feasible process. Prior to this discovery, such a drug load has not been commercially feasible or practicable to manufacture. The DXM pellets herein possess a uniform coating, with uniform solubility, and importantly, have a uniform release profile with low variability. Applicant's resultant product is also stable upon curing, and storage.

Applicants product is likely to be a stronger product than one produced by the process and Examples of the '712 patent. The product of the '712 Examples will not have as consistent a release profile as a product produced by Applicants. The release profile of a product produced by the process of the '712 patent will be slower and more variable, than that of Applicants for a similar % w/w load of functional coat.

The Examiner comments that the cited reference does "not teach the glass transition point of the ethyl cellulose dispersion. However, it is the Examiner's position

that the particular glass transition temperature is inherent because the reference teaches use of the claimed ethyl cellulose dispersion, namely, Surelease®".

Applicants found in their experimentation that the glass transition temperature of the product was not as predicted by the manufacturer. They in fact worked with the manufacturer over an extended period of time, and under extensive reaction conditions to find that under the particular dew point conditions of 9 +/- 5 C the Tg was about 38 to 41 C. Applicants dispute the Examiner contention that this is an inherent and readily determinable characteristic of an ethylcellulose dispersion. It is unknown what the Tg of any plasticized ethylcellulose dispersion under this reaction conditions would be, nor whether it would be useful to achieve the desired products. Further, it is not that one could establish a Tg of the dispersion so used, but that the Tg is utilized under the conditions herein to produce a product which is more uniform, more soluble, less variable, and has a more consistent release profile than a product produced by an analogous process, i.e. the '712 patent.

It is also noted that the '712 patent does not disclose use of micronized DXM. The '712 patent does not disclose that one should cure the finished pellets at the Tg of the ethylcellulose at an elevated temperature for about 1 hour.

Consequently, Applicants process and products produced thereby are not anticipated by the claims of the '712 patent.

Reconsideration and withdrawal of the rejection to the claims is respectfully requested.

### **Rejection under 35 USC §102**

Claims 1 to 9, 11 to 19, 21, 22, 24 to 28, 30 to 33, 41 to 49, 51, 53 to 55, 61 to 67, 71 to 74, 78, 93, and 94 are rejected under 35 USC §102(b) as being anticipated by Paradissis et al., US 5,133,974. Applicants respectfully traverse this rejection.

Paradissis et al., US 5,133,974 discloses a different manufacturing process from that of Applicants (or from that disclosed in the '712 patent). The '794 patent does use an inert sphere onto which a drug is loaded with a small amount of a binding agent (column 5, lines 38 to 40). The ethylcellulose as described in column 5, lines 40 to 49 is used as a binding agent here and not as the functional coat. The loaded sphere is then required to be coated with a layer of talc, from about 4 to about 20% w/w (column 6, lines 1 to 8). The resultant product, i.e. the coated talc sphere is then coated with a "dissolution modifying system", column 6, lines 19 to 26.

The '794 process does teach use of a spraying system as employed in the present invention, but uses an older coating pan process for applying the coating layers, see Example 1 (column 8) and column 7, lines 17 to 20. The '794 process also requires a minimum of 6 hours for drying at a higher temperature than that of Applicants, i.e. 80C.

The '794 claims do not anticipate Applicants process as Applicants do not utilize the required talc coating on the spheroid of 4 to about 20% w/w of talc. Also, the '794 patent does not disclose micronized DXM, nor an ethylcellulose dispersion having a particular Tg of 38 to 41 C. The '712 patent does not require processing conditions having a particular dew point.

Consequently, Applicants process and products produced thereby are not anticipated by the claims of the '712 patent. Reconsideration and withdrawal of the rejection to the claims is respectfully requested.

### **Rejection under 35 USC §103**

Claims 1 to 103 are rejected under 35 USC §103(a) as being unpatentable over Paradissis et al., US 5,133,973 in view of Adusumilli et al., US 5,595,758. Applicants respectfully traverse this rejection.

The '758 patent is relied upon by the Examiner for a teaching of a combination of IR and SR drug particles. The Paradissis et al. '973 patent is relied upon for the reasons of record in the 102(b) rejection. The Examiner further states that "it would have been obvious for one of ordinary skill in the art to modify the sustained release formulation of Paradissis using the combination of drugs in view of the teaching of Adusumilli with the motivation of providing an oral dosage containing sustained release and immediate release of combination of drugs useful for the treatment of cold and sinus".

The '758 patent discloses a soft gelatin capsule, i.e. a delivery device, which is filled with an oil of choice and in which is suspended beadlets containing an active agent. Column 6, lines 51 to end provide for the ability to deliver two doses of two drugs. All the '758 patent indicates is that one of them "is an immediate release of the entire dose of one of the drugs, loading dose of the other drug and the maintenance dose of the other drug in a continuous release mode". The '758 patent is silent as to how a skilled artisan would make an active having differing release profiles. There is no teaching or suggestion in the '974 Paradissis patent which would direct the skilled artisan to expect that the '973 dosage form would be suitable for inclusion in the delivery device of the '758 patent. The '974 Paradissis patent is discussed in detail in the 102(b) rejection above and is incorporated herein.

The technology of Applicants invention and that of the Paradissis patent is simply to produce a beadlet which has certain release characteristics. Applicant's process and product are not relying on a particular delivery device for admixture of the actives, each of which have their own release profile.

The teachings of the '758 patent do not overcome the missing elements of the '973 patent in teaching or suggesting Applicants claimed process herein. The '973

patent does not suggest the spraying techniques as disclosed herein to achieve a product having the stability, release profiles, and increased drug loading of DXM as claimed.

The '758 patent does not discuss nor disclose use of micronized dextromethorphan to improve drug load. Claim 84 as originally presented (and now amended) is not disclosed nor suggested by the '758 patent, nor the '973 patent. Claims 85 to 92, dependent upon claim 84 are not taught nor suggested by either the '758 or the '973 patent, alone or in combination.

The specific AUC's, Cmax, and Tmax of the various figures of Claims 68 to 83 are not disclosed nor suggested by the '758 or the '973 patent, alone or in combination.

The use of a medium chain triglyceride as a plasticizer (claims 104 and 105) is not taught nor described by the '758 or the '973 patent, alone or in combination.

Claim 24 which requires micronized dextromethorphan and an ethylcellulose dispersion having a particular Tg is not taught nor suggested by the '758 or the '973 patent, alone or in combination.

Therefore, reconsideration and withdrawal of the rejection to the claims under 35 USC §103 is respectfully requested.

### **Rejection under 35 USC §103**

Claims 1, 10, 11, 20, 25, 39, 41, 50, 59, 68 to 70, and 80 to 92 are rejected under 35 USC §103(a) as being unpatentable over Oshlack et al., US 5,472,712 in view of Sparks et al. Applicants respectfully traverse this rejection.

Applicants have discussed in detail the '712 patent above and incorporate those comments herein. The '588 patent does not address the deficiencies of the '712 patent as to curing time, or the requirement of a high humidity for curing.

The '712 patent does not discuss nor disclose use of micronized dextromethorphan to improve drug load. Claim 84 as originally presented (and now amended) is not disclosed nor suggested by the '712 patent, nor the '588 patent. Claims 85 to 92, dependent upon claim 84 are not taught nor suggested by either the '712 or the '588 patent.

The specific AUC's, Cmax, and Tmax of the various figures of Claims 68 to 83 are not disclosed nor suggested by the '712 or the '588 patent.

Consequently, it is not believed that the '712 or the '588 patent alone or in combination render the claimed subject matter unpatentable. Reconsideration and withdrawal of the rejection to the claims under 35 USC §103 is respectfully requested.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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